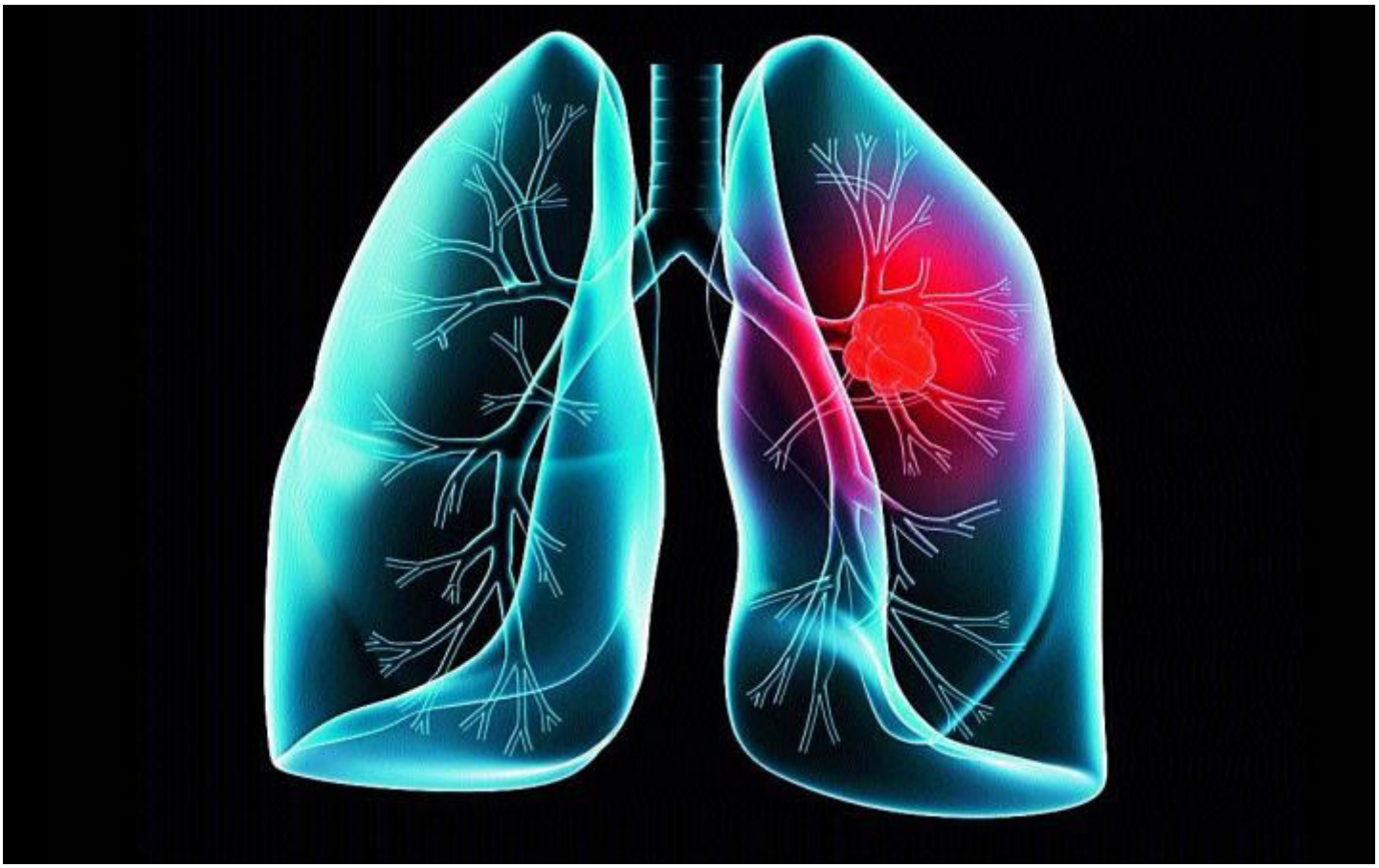
# Lung Deposition Models for Exposure and Risk assessment

CHRISTIAN LEJON



FOI-R--4753--SE
ISSN 1650-1942 March 2019

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| Titel | Lung Deposition Models for Exposure and Risk assessment |
| Title | Lungdepositionsmodeller för exponering och riskbedömning |
| Rapportnr/Report no | FOI-R--4753--SE |
| Månad/Month | March |
| Utgivningsår/Year | 2019 |
| Sidor/Pages | 22 p |
| Kund/Customer | Försvarsdepartementet |
| Forskningsområde | 2. CBRN-frågor och icke-spridning |
| FoT-område | Ej FoT |
| Projektnr/Project no | A406418 |
| Godkänd av/Approved by | Åsa Scott |
| Ansvarig avdelning | CBRN-skydd och säkerhet |

Cover photo: https://www.deccanchronicle.com/lifestyle/health-and-wellbeing/041217/how-air-pollution-causes-lung-cancer.html

# Sammanfattning

Inom projektet Effektmodeller vid FOI finns ett befintligt övergripande modelleringssystem för hotbilder där människor exponeras för ett CBRN-ämne inom vilket en lungdepositionsmodell ska implementeras. I detta arbete kartläggs för- och nackdelar med olika existerande lungdepositionsmodeller och redogörs för tillämpningsområden med avseende på användning i det övergripande modelleringssystemet. I kedjan Exponering – Dos – Respons reflekterar dosmängden deponerade partiklar i lungan. Modellen bör uppskatta deponering i lungan som funktion av partikelstorlekar samt även beskriva hur depositionen är distribuerad i andningssystemet, då båda dessa faktorer kan påverka de medicinska följderna av exponeringen. Det bör även finnas ett solitt ramverk kopplat till modellen som beskriver toxisk verkan av den deponerande mängden.

Den tillgängliga exponeringsarean för hud är ca 1,5 - 2,0 $m^2$, mag- och tarmkanalen utgör ca 200 $m^2$ och lungorna ca 140 $m^2$. Eftersom partiklar snarare inhaleras än sväljs, utgör lungorna den mest kritiska exponeringsvägen. Vuxna människor andas in över 10 000 liter luft per dygn, vilket ger upphov till en potentiellt hög exponering via lungorna. För att kunna prediktera effekterna från en given aerosol är det således av yttersta vikt att bedöma deponerad mängd i luftvägarna. Tänkta scenarier för bildande av partikulär aerosol kan vara vid brand, läckande tank eller en härdsmälta. Det kan också vara ett avsiktligt spridande av ett CBRN-ämne genom luftburen aerosol, även om det är mindre vanligt.

Baserat på den genomsökta litteraturen visar det sig att vilken som är den mest lämpliga modellen beror på aerosolen i fråga. I korthet: aerosoler som bär radioaktiv isotop modelleras bra med ICRP:s modell, nanopartiklar (vare sig de är radioaktiva eller inte) med NCRP:s modell, farmaceutiska aerosoler med MCNP-modellen och för detaljerad forskning finns flera alternativ att bygga på.

Nyckelord: Lungdepositionsmodeller, aerosol

## Summary

This report the concerns the implementation of a lung deposition model into an existing modelling system within the project Effect Models at FOI, the Swedish Defence Research Agency. In the chain Exposure-Dose-Response, dose is herein the amount of aerosol deposited in the lung. The model should be able to estimate the deposition as a function of particle size and the distribution of the deposited particles in the respiratory system. Both these two factors may have impact on the medical consequences following the exposure. Effect Models deals with scenarios including human exposures to particulate aerosols. The available human body exposure area to airborne particles is for the skin 1.5-2 $m^2$, the gastro-intestinal 200 $m^2$, and respiratory tract 140 $m^2$. Adults breathe over 10 000 liters of air every day and since aerosols are rather inhaled than swallowed; the lungs are the major route of concern for atmospheric spread of toxic agents. To accurately assess health effects (the response), it is of uttermost importance to predict lung deposition in the various regions of the respiratory tract. Example of scenarios that unintentionally may produce toxic particulate aerosols include fire, leaking tanks or nuclear meltdowns. Other cases, although less common historically, include intentional atmospheric spread of chemical, biological or radio nuclear agents. It was found that the most suitable model depends on the aerosol at hand. In brief; radioactive aerosols are best modeled with the ICRP model, accurate nanoparticle deposition can be obtained with NCRP model, pharmaceutical aerosols can be evaluated with the MCNP, and several alternatives exists for research details.

Keywords: Lung deposition models, Aerosol

# Content

# 1 Introduction to lung deposition models

Particulate aerosols are liquid or solid particles, which normally exist in the atmosphere and in the air that humans inhale. Dose is in this context, is defined as the number or mass of particles deposited in the respiratory tract and gives either a radiological-, infectious-, or chemical dose. One should bear in mind that *"Any discussion of the deposition of atmospheric aerosol would be incomplete without a consideration of the influence of airborne co-contaminants on the lungs of the people inhaling the particles*" as Lippmann stated in a review of lung deposition models [1]. Thus, intimately related to lung deposition models are clearance models and dose-response models. Examples of hazardous aerosols are chemical aerosols including inorganic materials, metals, fibrous materials such as asbestos, or emerging nanomaterials like carbon nanotubes [2, 3, 4]. A normal dust aerosol can also be a carrier of something much more potent, e.g. radioactive material. Deposition models for biological aerosols have been and are still scarce.

Prerequisites for lung deposition will be the physical data of the aerosol, as well as the physiological conditions of the person that is exposed. The physical data include size, concentration, density and shape of the particles and may stem from measurements or dispersion calculations. Physiological conditions determine the airflow properties in the respiratory system, which are indirectly given by exercise level, age, and gender. The most important factor determining the dose is the level of exposure, i.e. the concentration and duration of exposure to the aerosol. Lung deposition models by definition do not consider absolute deposited dose but rather the fraction of particles of a given size, shape and density that is deposited at a given place in the respiratory system. This is a review of different deposition models and comments on their applicability in an exposure and risk assessment perspective.

# 2 Brief history

Toxicity of inhaled particles is first documented in 1700 as occupational hazard [5]. The history of lung deposition models started however in the 1930's with the Findeisen model [5]. The four basic elements of a lung deposition model are morphometry of the respiratory tract, respiratory physiology, flow pattern, and particle behaviour in that flow. The Findeisen model is a so-called compartment-in-series-model, which treats the respiratory tract as a series of (nine) different compartments, from the trachea to the alveoli. The mechanisms considered most important, are essentially the same as those considered today, inertial impaction, gravitational settling, diffusion and interception. Although the Findeisen model substantially have the same form as many modern models, it suffers from two major physical inconsistencies. The entire inhaled volume reaches all compartments and particles do not deposit during exhalation.

An important step was taken at the Chalk River conference in 1949 in Canada [6]. The need for standardized values for workers exposed to aerosols in a radioactive contaminated area were discussed. It was agreed on a very simple model that 50% of inhaled particles reached the alveoli. Unless the particles were soluble, half of the deposited fraction (i.e. 25%) was retained in the lung indefinitely and the other half was assumed to be cleared by mucociliary action in the upper airways. Soluble particles were modelled to be fully retained for radiological dose estimation purposes. In the International Commission on Radiological Protection (ICRP) Publication 2 in 1960, a simple time dependency of the clearance rate was also included.

The next major improvements were made by Landahl in 1952. The mouth, larynx and extra orders of alveolar ducts were included a well as deposition during exhalation. The Findeisen model with Landahl's additions is essentially, what ICRP adopted for their second model published in 1979 [5, 6]. For the radiological community, it was a major improvement to include particle size dependence, respiratory rate, and regional deposition.

From the early lung deposition models, refinements have been made in several aspects such as improved lung morphometric measurements, more detailed flow patterns and more detailed deposition patterns. In difference to ICRP, occupational exposure guidelines to chemical aerosols do not in general explicitly include models for lung deposition, but are based on the fractions of aerosols classified as inhalable, thoracic or respirable [7]. Nevertheless, we believe that the accuracy of an occupational hazard assessment can be improved with lung deposition models. It is of utmost importance that a deposition model is coupled to the induced effects in the human. For radiological substances, such models that couple deposited dose of particles to biological effects in humans, are already in place within the ICRP framework, but models for chemical and biological responses needs to be developed.

# 3 General aspects of lung deposition

The available human body exposure area to airborne particles is for the skin 1.5-2 $m^2$, the gastro-intestinal 200 $m^2$, and respiratory tract 140 $m^2$ [8]. Adults breathe over 10 000 litres of air every day [9], rendering the respiratory system a very important component in aerosol exposures.

The deposition of particles can be understood by determining

1. the airflow in the respiratory tract
2. the behaviour of particles in that airflow.

For details on the subject, the reader is referred to an excellent review by Chiu-sen Wang [10] and references therein; however, a glimpse is given here.

The general approach to derive flow properties in the various parts is to solve the Navier-Stokes equation under mass conservation of simplified geometries, such as straight cylindrical segments. No-slip boundary conditions are applied on the airway walls (velocity is zero) but with specified inlet/outlet conditions. The pressure and velocity values as well as their gradients are chosen to fit the problem. Typically, parabolic velocity profiles in the conducting airways are chosen and the lengths of the airway walls are assumed to be long enough for fully developed flow profiles. In the nose and mouth, the flow is characterized by turbulence, but it transits to a mixed state of a jet, a recirculation and a secondary flow in the pharynx, larynx and trachea. Further down in the respiratory bronchioles and alveoli, laminar flow develops [10].Turbulent flow disturbs the boundary layer or depletion zone, and deposition enhances as it brings particles from high concentration closer to the airway walls. Lung morphometry is obtained from casts [11] despite only the upper airways has been accurately measured. The limited availability of such data is a limiting factor to obtain accurate lung deposition models [12]. Airflow varies with e.g. lung morphometry (i.e. age and gender) and the level of physical activity. It also varies between individuals because of size difference of the airway dimensions as well as lung diseases such as asthma or chronic obstructive pulmonary disease (COPD), causing a dysfunctional lung and hence deposition patterns are changed.

The major factors describing particle deposition include inertial impaction, diffusive transport, gravitational settling, and interception. Mathematical formulations for these transport mechanisms based on force-equilibrium equations are available and can be readily applied [10, 13]. Different authors have derived various forms of deposition equations, however the largest uncertainties to deposited fractions are still related to anatomical variations [14] rather than the model itself. Deposition is largely determined by the particle size and the processes must be combined to derive the total deposition velocity. Particles larger than approximately 1 µm deviates mainly from a curved streamline path because of inertial motion and may therefore impact on an airway wall. Gravitational settling is also relevant to larger particles as they carry greater mass, particularly in the alveolar region, where the residence time is increased and the airway dimension decreased. Diffusion of particles, also known as Brownian motion, is governed by Fick’s first law and results in a particle flux from high- to low concentration. It is the dominant factor for ultrafine particles, and for the same reasons as for gravitational settling, extra important in the alveolar region. Results from earlier research at FOI is shown in Figure 1, and shows an electron micrograph of deposited nanoparticles in the alveoli of a rat.

Compared to the other mechanisms, interception is not an active transport of particles, but rather related to the finite size of particles. The particle trajectory follows a streamline that is so close to an airway surface that the particle adhere to the airway wall. This is particularly relevant to fibrous material.

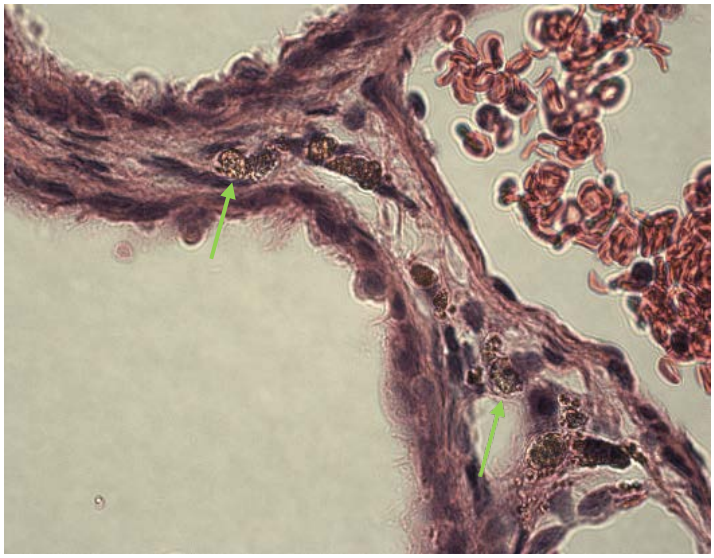

**Figure 1**. Previous research at FOI: Electron micrograph of deposited nanoparticles in the alveoli. Aggregates of primary nanoparticles, indicated by green arrows, are found within the epithelial layer of oval cells.

Clearly, modelling the deposition of particles in the lung is a complex problem as it involves different flow types and forces acting on the particles. Experimental studies is a way to circumvent uncertainties in theoretical modelling, however, data is often limited to specific breathing patterns and particle sizes [6, 15]. Total (whole lung) deposition can be studied by particle counting in a respiratory flow setup. Regional deposition can be studied with radioactively labelled particles. About 50 experimental studies that report on deposition of sub 300 nm particles have been presented. Many of the results are diverging because there is no standardized method or measurement protocol [16]. Nevertheless, with the recent advances in experimental setup more reliable comparisons can be made [17].

# 4 Existing lung deposition models

The published models are categorized into five different groups following Hofmann [12]. Lung morphology is perhaps the most important factor that affects deposition fractions and essentially all these five groups corresponds to different lung morphologies. The first group is semi-empiric models and they combine first principle mechanistic models with experimental data when available (e.g. the naso-pharyngeal region). The second group is continuous models or trumpet models which will become clear below. The other three groups are truly mechanistic models, i.e. deposition fractions are derived based on classical flow-equations in the respiratory tract model, followed by particle behaviour in that flow. They are also known as compartment-in-series-models in the sense that the anatomical regions are modelled in series with connecting flow, concentration and time properties. All these branching models describe the airways as tubes starting with trachea, which splits up into finer and finer airways that finally ends with the alveolar sacks. The way the splitting scheme is defined affects model characteristics and is the basis for the categorization below. Both Lagrangian, in which single particles are tracked, and Eulerian modelling concepts, where an ensemble or concentration of particles are tracked, are used [12]. Each of which has its pros and cons depending on the physics applied to the system. The Eulerian approach is preferable for smaller particles at high concentrations, while the Lagrangian approach is preferable in the opposite regime of fewer and larger particles.

## 4.1 Semi-empirical regional compartment models

The International Commission of Radiological Protection (ICRP) published in 1994 a “Human Respiratory Tract Model for Radiological Protection”, referred to ICRP66 [6]. This substantial work thoroughly goes through the important aspects of lung deposition and reviews, and at that point, the state-of-the art research in the field. This model can be thought of as a series of filters where each filter corresponds anatomically to regions of the respiratory tract. These regions of the ICRP model are outlined in Figure 2. The model has recently been updated in ICRP Publication 130 to account for the latest research, and the major step forward in this publication is the clearance models including clearance from alveoli to blood [18]. Deposition fractions are based on either theoretical considerations or adaptions to experimental data, and are derived from peer-reviewed published research. It includes adjustments for gender, ethnicity, age, physical activity level, nose or mouth breathing, hygroscopicity, and considers deposition from both inhalation and exhalation. These aforementioned parameters are relevant to all types of aerosols. The ICRP66 model also includes dosimetry of radioactive particles as it is the main goal for the committee. Furthermore, the only model for spread of infective disease related to inhalation of airborne agents is based on an extension of ICRP 66 [19].

Independently of the ICRP, the National Council on Radiation Protection and Measurements (NCRP) in the USA published another well-developed model [20] in 1997. Just like ICRP66, the NCRP-model considers the most important factors such as the level of physical activity, nose or mouth breathing, etc., as well as clearance and dosimetry models. The main difference between them is for ultrafine particles where NCRP considers another, later and presumably more correct, description of deposition that results in higher fractions in the naso-pharyngeal region [21]. Correspondingly, fewer ultrafine particles deposits in the pulmonary region, which from a toxicological perspective, is considered as the most important region. To the advantage of the ICRP model, the clearance models are more developed with several clearance mechanisms including transport into the blood from five different compartments, as pointed out in the ICRP 130 update [18].

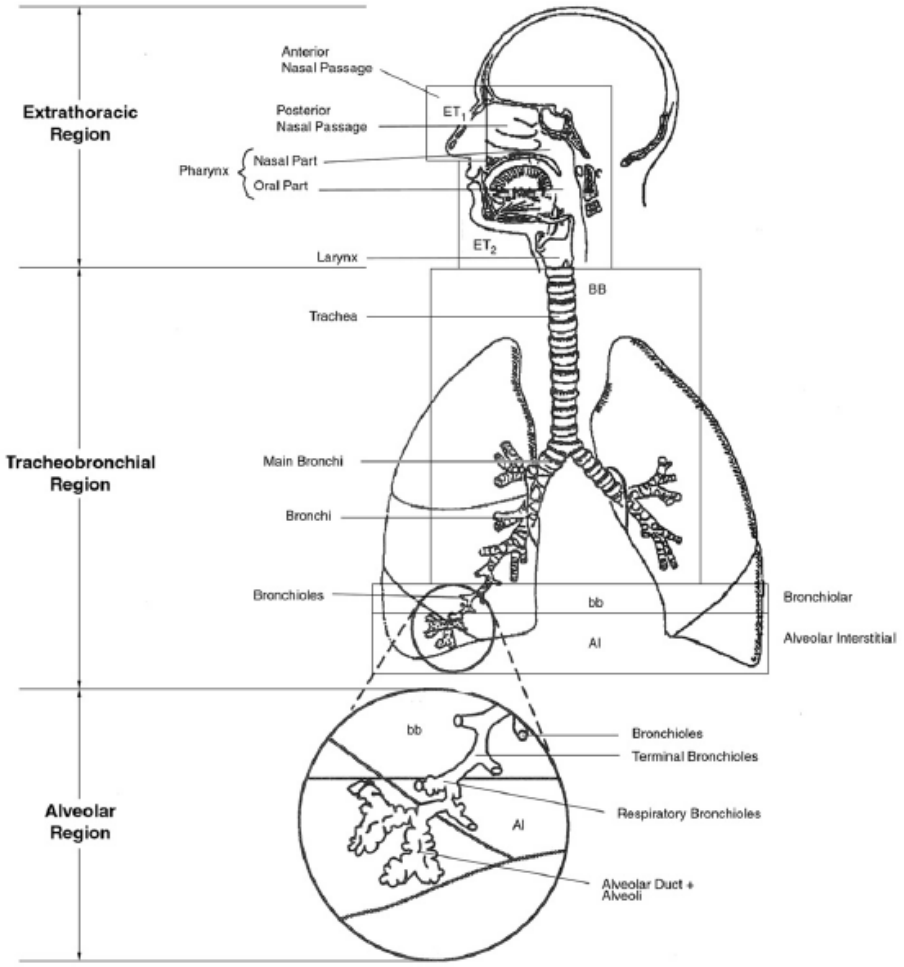


**Figure 2.** The ICRP [6] anatomical description of the respiratory tract where each of the abbreviations ET1, ET2, BB, bb, and AI constitutes a filter in the ICRP filter-in series model.

## 4.2 One-dimensional trumpet models

This is not a compartment-in-series model, which makes it unique in that respect. Breathing is instead compared to the flow of an aerosol through a trumpet-shaped conduit where the airway length from trachea is along the trumpet and the lung airway total cross-sectional area is pictured as the cross-sectional area of the trumpet. Particle balance equations are set up with loss terms for deposition due to diffusion, sedimentation, impaction etc., which results in a time and spatially dependent dynamics (differential) equation [12]. Trumpet models are truly mechanistic and do not rely on experimental data. Adding or modifying physical processes that affects deposition is relatively easy and one could say that trumpet-models are more suited for detailed research [15, 22], rather than for hands-on health assessments.

## 4.3 Deterministic symmetric branching or simple path models

In the simple path model, every splitting is assumed to be symmetric and by averaging over geometries, a typical path is derived. Thus all paths from trachea to every single alveoli behave in the same way, with respect to particle deposition. Since only lengths and diameters of 10-15% of the bronchiole have in fact been measured [23], the remaining airways deeper in the lung are assumed to have the same geometry in terms of branching

angle. This results in a computationally simple, but yet useful model. The shortcomings are mainly the lack of geometrical data in alveolar- ducts and sacks. Consequently, the variations in deposition in these regions in particular cannot be modelled. Some remedy of the geometrical shortcomings is taken care of by the introduction of typical paths for all five different lobes by Yee and Schum in 1980 [24]. This geometry is the base for the NCRP and ICRP models. Carcinomas have been reported to occur more frequently in the left than in the right lung and also in the upper than the lower parts [12]. Thus, these so called local- or regional scale models have their incentives. To this geometry, various first principles deposition- and flow equations are then applied, reflecting different breathing patterns and different models therefore arise. The Eulerian approach is common and the interested reader is referred to the excellent reviews written on the subject [9, 10, 12].

## 4.4 Deterministic asymmetric branching or multiple path models

The Yeh and Schum 1980 model [24] mentioned above with typical paths to each lobe can be seen as the first step towards human multiple path models. The advantage with asymmetric models is their ability to model lobar deposition. An early work with asymmetric deterministic branching is the one by Anjivel and Ashgarian in 1995, on a rat lung [25]. Deposition is calculated for every single airway. Depending on the conducting airway differences, a small fraction of the pulmonary acini was shown to receive twice the dose, witnessing on the variations of realistic air pathways in the same lung. The work is motivated by a need for site specific determinations, particularly in the alveoli, as carcinogenic effects are believed to relate to a threshold exposure level. One problem however, is that the complete asymmetry of the human lung is not deterministically described [12]. Based on the stochastic model of Koblinger and Hofmann in 1990 [23], ten structurally different five lobe asymmetric lungs were introduced in 2001, which is referred to as the MPPD (multiple path particle dosimetry) model. The MPPD is available for download, free of charge (see below) and it has been updated continuously, to accommodate clearance models, various dose-metric outputs, morphometries for mice, rats, rhesus monkeys, sheep and pigs [26]. Within MPPD, the aerosol is described by up to four lognormal particle size distributions (PSD), however, user described PSD’s is not implemented to my knowledge. It finds its application primarily within therapeutic aerosols and laboratory based research.

## 4.5 Stochastic asymmetric branching or stochastic multiple path model

In the Lagrangian model approach, the branching is still dichotomous with connecting cylindrical tubes, but allows for randomization of length, angles and diameters of the conducting airways, and these parameters are chosen from a probability distribution function that are based on physical measurements of Raabe 1976 [11]. This means, that for a given set of input parameters such as breathing patterns, ventilation rate, age, etc., the result is not necessary exactly the same for different runs because of the stochastically described conducting airway geometry. However, by simulation hundreds of thousands particles, statistically averaged deposition patterns can be derived. Stochastic models are more scientifically sound because they account for natural anatomic variations. The lower respiratory morphology could not be experimentally determined by Raabe in 1976, and these finer airways are assumed to follow the same structural relationships as the upper airways. One advantage with these models is that they can easily be adapted to the adult population in a broad sense by scaling linear measures according to variations of the measurable quantity Functional Respiratory Capacity (FRC). This stochastic model was presented in 1990 to 1992 and termed IDEAL-2 [27, 28, 29]. Some assumptions have to be made before modelling begins, it has been shown that the mixing factor (mixing of tidal and distal air volumes) and the alveolar diameter are the two most important parameters, and variations in their input values drastically affect the results in deposited fractions [28].

Until now, the IDEAL-2 model should still be considered as the best effort to theoretically bridge the gap between whole lung models and experimental data. Furthermore, the authors compared the derived results to, at that time, available experimental data with good agreement [14, 29]. Similar to the multiple path model, stochastic models are able to predict lobar deposition. These stochastically based lung morphology models have been extended to study special cases such as deposition of ultrafine particles, [30] hygroscopic growth [31], intersubject variability [32], and charged particles [33].

# 5 Deposition models compared

Hofmann has compared the five different models described above in the size range 1 nm to 10 µm for nasal inhalation under sitting breathing conditions [12]. He found that the total (i.e. the entire respiratory tract) deposition fraction of all models lie within ± 10% with a typical U-shaped form, caused by Brownian diffusion for particles below 0.1 µm, and gravitational settling and inertial impaction for particles above about 1 µm, Figure 3. This difference seems small with regards to the other factors relevant in the scenario such as concentration, time of exposure and size determination of the aerosol..

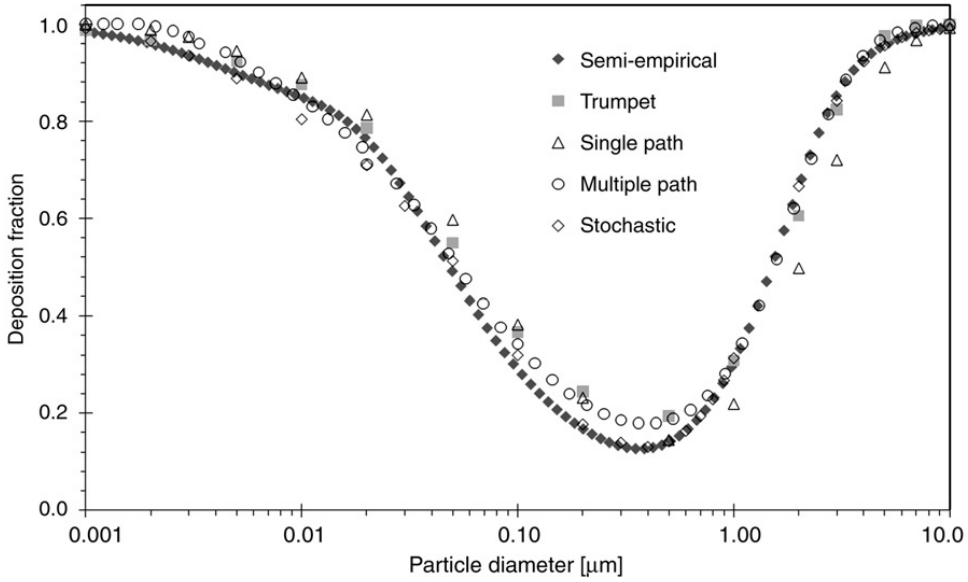


**Figure 3.** Adopted from Hofmann [12] Comparison of model predictions of total deposition of unit density particles ranging from 1 nm to 10 µm under nasal sitting breathing conditions applying five different deposition models: semi-empirical (ICRP 1994) [6], trumpet [3], single path [34], multiple path [23], and stochastic [27].

On the other hand, regional variations between models are more pronounced. According to the multiple path model, fine particles (<30 nm) are captured to a greater extent in the nasal region [12] and are therefore subject to other clearance mechanisms compared to if they were captured in the bronchial region. The difference is roughly 20% to the average of other models [12]. Therefore, the multiple path model also shows a correspondingly lesser deposition in the bronchial region as shown in Figure 4 panel a. The trumpet model also deviates with approximately 20% higher deposition in the bronchial region for ~50 nm particles. Systemic toxic effects are more strongly related to deposition in the acinus than to deposition in any other region [35]. The comparison by Hofmann shows that all models predict similar deposition fractions in the alveolar region with a span of about 15% in the size range 100-200 nm particles, as shown in Figure 4 panel b. However, a comparison between the two semi-empiric models NCRP and ICRP differs markedly in the ultrafine size range, due to enhanced diffusion in the NCRP model, and this should be considered as the more accurate model of the two.[21]

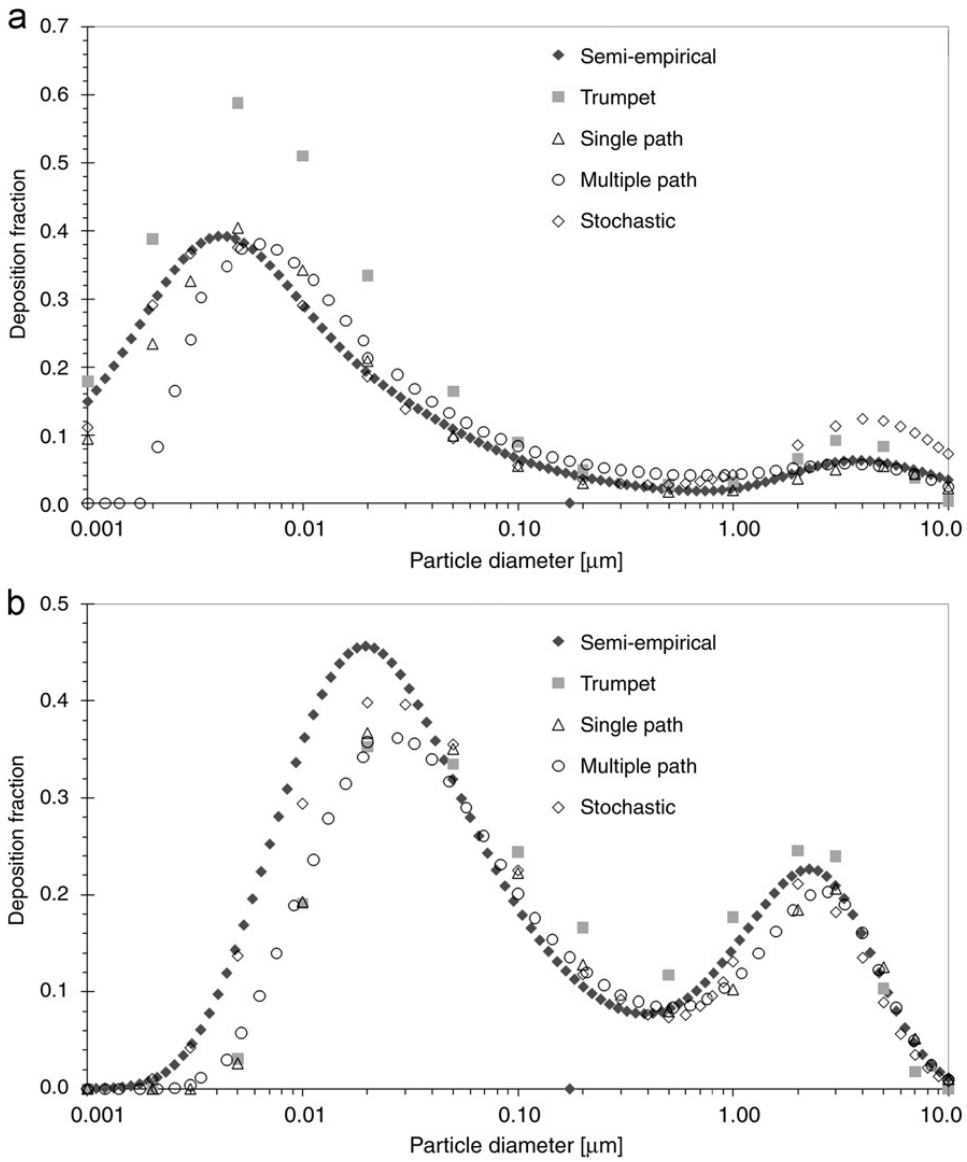


**Figure 4.** Adopted from Hofmann [12]. Comparison of model predictions of brochial (panel A) and acinar (panel B) deposition of unit density particles ranging from 1 nm to 10 μm under nasal sitting breathing conditions applying five different deposition models: semi-empirical (ICRP 1994) [6], trumpet [3], single path [34], multiple path [23], and stochastic [27].

# 6 Current state of the field

The overall greatest deficiency of all models is the lack of complete lung structure measurements. Few lungs have been measured, the alveolar structure could not be experimentally revealed, and models therefore use extrapolated data. Although straight tubes in the model described above simplify the morphology, they seem to give a fairly good agreement with experimental studies. However, the detailed deposition patterns in realistic morphologies could potentially increase understanding of local toxicological or radiological effects such as carcinomas.

Computational fluid-particle dynamics (CFPD), is a numerical method that nowadays is more frequently used to simulate deposition, particularly at sites of special interest, or of isolated complex geometries such as airway bifurcations, alveolar sacs [36], or the extrathoracic airways [37, 38, 39]. Although these CFPD results are not yet incorporated into any of the classical models, they do offer a deeper insight into deposition in more realistic airway configurations, and the results include turbulences and secondary flow profiles [12]. The deposition pattern of infants and children have recently been explored to a greater detail using CFPD techniques [40]. Complex and moving geometries are challenges to the simulations, and their validity needs to be established. In addition, whole lung models need to be developed.

Besides mapping the detailed flow pattern in the complex lung, the other major challenge is personalized deposition. Based solely on mechanistic models applied to measured nasal and oral [41] as well as whole lung dimensions [32], the inter-subject variability was estimated to 30-50 %. Experimental studies confirm these predictions [16] and besides lung structure the breathing pattern is assigned to be the most important predictors of deposition [42]. The model approach to accommodate personal variations is by scaling the linear airway dimension according to bodyweight and height. However, in exposure risk assessment the estimations of breathing pattern and ventilatory rates are anticipated to be a major source to the error of deposited amounts. An attempt has been made to adapt structural airway units of cystic fibrosis patients [43].

Co-imaging with different types of gamma cameras, such as SPECT and PET scans, to reveal both anatomical information as well as deposition of radioactive labelled test aerosols [44], is now advancing to synchrotron radiation based computational tomography [45]. Although these techniques are primarily for diagnosis and to follow progression of COPD, they may in the future serve to shed light on individual deposition in the otherwise so inaccessible respiratory system of living persons.

Hygroscopicity of particles is shown to have a great effect on deposition. When hygroscopic particles enters the humid airway they grow as water vapour condense on their surface [31].This phenomenon was excellently modelled by an extension of the MPPD model, and variations of 0.4 units of deposited fractions was observed [31]. Far from all aerosols are hygroscopic, but several models do not account for hygroscopic growth within the lung.

# 7 Implementations and hardware

A recent open-source implementation ICRP model can be found on github [46]. As the semi-empirical models are based on algebraic equations, they can be run on a normal office computer. Simple path models are inherently computationally low intensive, but the more complex the geometry is the higher computation requirements. The multiple path model (MPPD) [26] also run on office computers and is available online free of charge (http://www.ara.com/products/mppd.htm). CFPD-models are more computationally expensive and rely on third party software [47]. No implementation of the IDEAL-2 model have been found nevertheless the algorithm is described in the original work [27].

# 8 Choice of model

In light of applying models to particles carrying C, B, or RN substances and risk assessment, it is of utmost important that a deposition model can be coupled to the induced effects in human. Clearance models must be coupled with the deposition fractions. Availability of dose-response models or relations sets a constraint on which a deposition model is suitable in risk and exposure assessment. Models relying on more complicated lung structure (stochastic) models are better suited for research and they do better agree with experimental data because of their more realistic morphological description. On the other hand, in semi-empirical models, adaptions of simple algebraic equations to experimental data, when available, are already done. If data is not available, the most accurate theoretical considerations are used. For the reason of good coupling to response and clearance models and that they cover a broad range of different scenarios of the general public, the ICRP model is recommended to be implemented for risk- and exposure assessment in the project Effect Models.

Biological aerosols have not been extensively modelled in the lung deposition models presented herein. The only work found, builds on the ICRP model [19]. Modelling transmission of infectious disease is beyond the scope of this work as it involves several other aspects than lung deposition [48].

Radiological aerosols are definitely best modelled with either NCRP or ICRP model because of the well-developed systemic models following exposure. Unless high accuracy in deposition fractions in the alveolar region of ultrafine particles is priority, the ICRP model is recommended because of the associated models of transport to blood. Be aware that these models are developed for long-term effects and not acute effects, as they derive averaged organ dose. The MPPD is an alternative for acute local effects as it was developed for threshold effects [46].

Chemical aerosols are either wet or dry physical particles that are dispersed in air but do not carry biological or radioactive material. Hence, it is a broad group of substances ranging in toxicity from highly acute toxic chemicals to less harmful ones; all the way to non-toxic natural aerosols, (for example sea salt sprays along the coastline). In any case, accurate clearance models are required in risk assessment. As the greatest variations in deposition fractions stems from different lung morphologies, the model should account for variations in age, gender, physical exercise level and nose vs. mouth breathers among members of the public. The only models that fulfil these criteria are the MPPD, ICRP, and NCRP. For acute toxicity, the MPPD model is worth considering, and for accurate nanoparticle deposition, the NCRP is recommended. Otherwise, the ICRP is recommended for its extensive and recent reviewing.

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